(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
26 June 2003 (26.06.2003)

PCT

(10) International Publication Number
WO 03/051408 A1

(51) International Patent Classification[7]: A61L 15/24, C08F 20/58

(21) International Application Number: PCT/GB02/05681

(22) International Filing Date:
13 December 2002 (13.12.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

0130369.2	19 December 2001 (19.12.2001)	GB
0205702.4	11 March 2002 (11.03.2002)	GB

(71) Applicant *(for all designated States except US)*: **FIRST WATER LIMITED** [GB/GB]; Hilldrop Lane, Ramsbury, Marlborough, Wiltshire SN8 2RB (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **MUNRO, Hugh, Semple** [GB/GB]; Barton Cottage, Weston Sub Edge, Chipping Camden, Warwickshire GL55 6QT (GB). **CERDAN, Carine** [GB/GB]; 47 Ockley Brook, Didcot, Oxfordshire OX11 7DR (GB). **HOSKINS, Richard** [GB/GB]; 68 Stafford Street, Swindon, Wiltshire SN1 3PF (GB).

(74) Agent: **BROWN, David, Leslie**; Haseltine Lake, Imperial House, 15-19 Kingsway, London WC2B 6UD (GB).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 03/051408 A1

(54) Title: HYDROGEL COMPOSITIONS COMPRISING AN ACRYLOYL MORPHOLINE POLYMER

(57) Abstract: The invention provides a hydrogel composition comprising a plasticised cross-linked hydrophilic polymer of acryloyl morpholine and optionally one or more comonomers.

HYDROGEL COMPOSITIONS COMPRISING AN ACRYLOYL MORPHOLINE POLYMER

Field of the Invention

The present invention relates to hydrogel compositions, and more particularly to hydrogel compositions suitable for use in wound and burn dressings, biomedical electrodes and other applications where skin compatability is required. The invention also relates to a process for the manufacture of the novel hydrogel compositions.

The expressions "hydrogel" and "hydrogel compositions" used herein are not to be considered as limited to gels which contain water, but extend generally to all plasticised gels and gel compositions, including those containing a non-aqueous plasticiser.

Background of the Invention

Cross-linked hydrogels based on hydrophilic acrylamido polymers have been previously described by Laskey (US Patent No. 3929741, the disclosure of which is incorporated herein by reference) and others. The ability of these materials to imbibe large quantities of aqueous liquid (e.g. water, biological fluids) and to retain their structural integrity was considered to be advantageous in a number of biomedical and consumer applications (Laskey, column 3, lines 36 to 57).

Subsequent to Laskey, a large amount of research has been conducted into cross-linked hydrogels based on acrylamido polymers for use as skin adhesives for a range of applications including biomedical electrodes and wound dressings. Representative references include PCT Patent Applications Nos. WO-00/06214, WO-00/06215, WO-00/07638, WO-00/46319 and WO-00/65143, the disclosures of which are incorporated herein by reference.

PCT Patent Application No. WO-01/96422 (the disclosure of which is incorporated herein by reference), which was published after the priority date of

the present invention, describes a process for the manufacture of a high water content cross-linked hydrogel composition, comprising:

(i) preparing a mixture comprising:

(1) one or more unsaturated free-radically photo-polymerisable monomer capable of polymerisation to a hydrophilic polymer;

(2) one or more free-radical photoinitiator;

(3) one or more cross-linking agent comprising a multifunctional unsaturated free-radically photo-polymerisable compound; and

(4) water; and

(ii) irradiating the mixture with light of sufficient intensity and at an appropriate wavelength to polymerise and cross-link the mixture to form the composition;

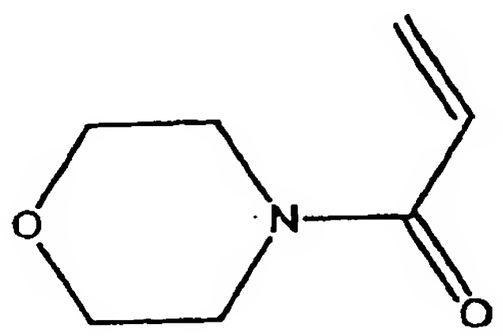
wherein substantially all of components (1) to (4) present in the mixture in step (i) are also present in the composition resulting from step (ii), the photoinitiator (2) is present in the mixture in step (i) in an amount between about 0.002% and about 0.05% by weight of the total mixture, and the cross-linking agent (3) is present in the mixture in step (i) in an amount less than about 0.5% by weight of the total mixture.

In PCT Patent Application No. WO-01/96422, it is stated that the expression "monomer" includes ionic and non-ionic monomers and monomer mixtures, and that, correspondingly, the expressions "polymerise", "polymers" and like expressions include both homopolymerisation and copolymerisation, and the products thereof. It is also stated that in one embodiment a non-ionic water soluble monomer will comprise at least one of acrylamide or a mono- or di-N-alkylacrylamide or an analogue thereof, the term "analogue" in this context referring to to non-ionic water soluble monomers containing an alkyl or substituted alkyl group linked to a carbon-carbon double bond via an amido or alkylamido (-CO.NH- or -CO.NR-) function. Examples of such analogues are

stated to include diacetone acrylamide (N-1,1-dimethyl-3-oxobutyl-acrylamide), vinyl lactams, N-alkylated acrylamides, N,N-dialkylated acrylamides, N-vinyl pyrrolidone and acryloyl morpholine. However, in all the Examples of PCT Patent Application No. WO-01/96422, the sole monomer present in the polymerisation reaction is sodium 2-acrylamido-2-methylpropane-sulphonate (NaAMPS).

Brief Description of the Invention

The present invention is based upon our unexpected finding that the acryloyl morpholine, and particularly the compound N-acryloyl morpholine (ACMO), which has the formula:



(I)

may be used as the base monomer in the preparation of a wide range of hydrogels, providing considerable technical advantages compared to known compositions.

According to a first aspect of the present invention, there is provided a hydrogel composition comprising a plasticised cross-linked hydrophilic polymer of acryloyl morpholine and optionally one or more comonomers.

According to a second aspect of the present invention, there is provided a process for the preparation of the hydrogel composition of the first aspect of the invention, the process comprising free-radically polymerising a mixture comprising (1) acryloyl morpholine and optionally one or more comonomer and (2) one or more cross-linking agent comprising a multifunctional unsaturated free-radically polymerisable compound; the polymerisation being conducted in the presence or absence of a plasticiser, with the proviso that when the polymerisation is

conducted in the absence of a plasticiser, a plasticiser is added to the polymer product of the polymerisation.

In the present invention, the acryloyl morpholine may be N-acryloyl morpholine, 1-acryloyl morpholine or 2-acryloyl morpholine, most particularly N-acryloyl morphiline.

The pre-polymerisation reaction mixture (pre-gel) preferably includes the monomer(s) at a total monomer level of from about 5% to about 70% by weight of the total pre-polymerisation mixture, more particularly from about 10% to about 60% by weight, most preferably from about 15% to about 50% by weight.

The pre-gel may, if desired, contain entrained air bubbles. The air bubbles may suitably be introduced into the pre-gel by mecahnical agitation, e.g. stirring, of the pre-gel. Introduction of the air bubbles typically precedes forming the pre-gel into the desired configuration for curing (e.g. before casting when it is intended to form a sheet hydrogel). On curing of the pre-gel, a hydrogel mass having an internal cellular structure, e.g. a foam, is formed. It is preferred that the pre-gel for a hydrogel having an internal cellular structure contains a surfactant, e.g. in an amount of up to about 10% by weight, more preferably between about 1 and about 10% by weight, more typically about 2% by weight.

When the polymerisation is conducted in the presence of a plasticiser, one or more different plasticiser and/or more of the same plasticiser may, if desired, be added to the polymer product of the polymerisation.

The plasticiser may be selected from aqueous and non-aqueous systems. Water or a mixture of water and a water-miscible organic plasticiser may suitably be used as an aqueous plasticiser. When a non-aqueous plasticiser is used, it may suitably be an organic plasticiser.

To the extent required by law, the above statements of the present invention shall be taken to exclude subject-matter which is unpatentable in view of the disclosure contained in PCT Patent Application No. WO-01/96422.

The hydrogel composition of the present invention may include one or more additional ingredients, which may be added to the pre-polymerisation mixture or the the polymerised product, at the choice of the skilled worker. Such additional ingredients are selected from additives known in the art, including, for example, water, organic plasticisers, surfactants, polymers, electrolytes, chloride sources, bioactive compounds, personal and body care agents, and mixtures thereof. The hydrogel composition of the present invention preferably consists essentially of a cross-linked hydrophilic polymer of acryloyl morpholine and optionally one or more comonomers, together with water and/or one or more organic plasticiser, and optionally together with one or more additives selected from surfactants, polymers, electrolytes, chloride sources, bioactive compounds, personal and body care agents, and mixtures thereof, with less than about 10% by weight (suitably less than about 5% by weight) of other additives.

The hydrogel composition may suitably be present in the form of a sheet having first and second major faces, each of said first and second major faces being in contact with a protective release layer, for example siliconised plastic or paper. Alternatively, the hydrogel composition may be present in the form of a sheet having first and second major faces, one of said first and second major faces being in contact with a protective release layer, for example siliconised plastic or paper, and the other of said first and second major faces being in contact with a backing member, suitably a backing member forming part of a wound or burn dressing, a biomedical electrode or another article where a bioadhesive hydrogel layer is to be provided in use between the article and the skin of a wearer. Still further, the hydrogel composition may be present in the form of a sheet having a woven or non-woven fabric, or a net, embedded therein.

The hydrogel sheets may typically have a thickness in the range of about 0.2 mm to about 2 mm. When such sheets are in contact with a release sheet, for example

a sheet of plastic or coated plastic (e.g. siliconised plastic) or paper or coated paper (e.g. siliconised paper), the hydrogel composition may suitably be coated at a surface weight of hydrogel in the range of about 0.5 kg/m^2 to about 2.5 kg/m^2.

For the preparation of a hydrogel composition in the form of a sheet, the process according to the invention may include initially forming a sheet of the pre-gel, and subsequently carrying out the polymerisation step so that the sheet hydrogel is formed *in situ* by the polymerisation reaction. Most preferably, material is not substantially added to or removed from the resultant hydrogel composition, although in some cases some degree of subsequent conditioning and/or modification may be desirable.

When the hydrogel composition contains water, it may for some applications be classed as a high water content hydrogel composition, the expression "high water content" referring particularly to hydrogel compositions comprising more than about 40% by weight of water, more particularly above about 50% by weight, and most preferably between about 60% and about 95% by weight.

The expressions "comonomer", "monomer" and like expressions used herein include ionic and non-ionic monomers and monomer mixtures. Correspondingly, the expressions "polymerise", "polymers" and like expressions include both homopolymerisation and copolymerisation, and the products thereof.

The acryloyl morpholine monomer is a liquid at room temperature, and is chemically non-ionic. We have found that the quality of the hydrogel composition is generally good across a wide range of monomer and plasticiser amounts. We have found that the quality may suffer - with unacceptable brittleness and syneresis of the plasticiser - at high levels of organic plasticiser, for example above about 50% by weight organic plasticiser. This problem can, however, be overcome by incorporation of a small amount (e.g. up to about 10% by weight, more particularly up to about 5% by weight) of an ionic comonomer in the pre-gel.

We have also found, surprisingly, that hydrogel compositions based on ACMO can be unusually tolerant of extremes of ambient temperature and atmospheric dryness. In other words, the hydrogel will maintain its properties to an acceptable extent and for extended periods of time at very much lower or higher temperatures than room temperature (e.g. between about -10°C and about +30°C), and under a substantially bone dry or fully humid atmosphere. This renders the compositions useful in extreme environments, such as arctic and desert conditions. To prepare such hydrogel compositions, it is preferred that the pre-gel is formed as an aqueous composition containing a salt in substantial saturation or supersaturation in the pre-gel. This may conveniently be achieved by initially warming a hydrated form of the salt to a temperature at which the salt melts or dissolved in its water of crystallisation, and adding the ingredients of the pre-gel to the liquid thus formed. The elevated temperature, which may typically be up to around 60°C, may then be maintained or allowed to slowly fall, to maintain or increase the extent of the saturation or the supersaturation, before the pre-gel is cured by the polymerisation reaction.

Detailed Description of the Invention

Hydrogel Composition

The hydrogel composition of the present invention comprises a plasticised three-dimensional matrix of cross-linked polymer molecules, and has sufficient structural integrity to be self-supporting even at very high levels of internal water content, with sufficient flexibility to conform to the surface contours of the human skin. Where the intended use of the hydrogel is in biomedical electrodes, wound dressings, and other applications where skin adhesion is desired, the hydrogel composition preferably has sufficient bioadhesion to adhere to the skin under all skin and moisture conditions likely to be encountered during use. Our PCT Patent Application No. WO-00/45864, the disclosure of which is incorporated herein by reference, describes a method whereby the skin adhesion performance of the hydrogel can be predicted and thereby tailored to particular applications.

The hydrogel compositions with which the present invention is concerned generally comprise, in addition to the cross-linked polymeric network, an aqueous plasticising medium and, where electrical conductivity is required, at least one electrolyte, whilst the materials and processing methods used are normally chosen to provide a suitable balance of adhesive and electrical properties for the desired application.

Ionic Comonomer

The one or more ionic comonomer, if present, will be water soluble and may be selected from: 2-acrylamido-2-methylpropane sulphonic acid or an analogue thereof or one of its salts (e.g. an ammonium or alkali metal salt such as a sodium, potassium or lithium salts); acrylic acid or an analogue thereof or one of its salts (e.g. an alkali metal salt such as a sodium, potassium or lithium salt); and/or a polymerisable sulphonate or a salt thereof (e.g. an alkali metal salt such as a sodium, potassium or lithium salt), more particularly acrylic acid (3-sulphopropyl) ester or an analogue thereof, or a salt thereof. The term "analogue" in this context refers particularly to substituted derivatives of 2-acrylamido-2-methylpropane sulphonic acid, of acrylic acid or of acrylic acid (3-sulphopropyl) ester.

A particularly preferred ionic comonomer is a sodium salt of 2-acrylamido-2-methylpropane sulphonic acid, commonly known as NaAMPS, which is available commercially at present from Lubrizol as either a 50% aqueous solution (reference code LZ2405) or a 58% aqueous solution (reference code LZ2405A) and/or acrylic acid (3-sulphopropyl) ester potassium salt, commonly known as SPA or SPAK. SPA or SPAK is available commercially in the form of a pure solid from Raschig.

Non-ionic Comonomer

The one or more non-ionic comonomer, if present, may preferably be water soluble and be selected from acrylamide or a mono- or di-N-alkylacrylamide or an analogue thereof. The term "analogue" in this context refers to non-ionic water soluble monomers containing an alkyl or substituted alkyl group linked to a

carbon-carbon double bond via an amido or alkylamido (-CO.NH- or -CO.NR-) function. Examples of such analogues include diacetone acrylamide (N-1,1-dimethyl-3-oxobutyl-acrylamide), vinyl lactams, N-alkylated acrylamides, N,N-dialkylated acrylamides and N-vinyl pyrrolidone.

Cross-linking Agents

The cross-linking of the hydrophilic polymer in the hydrogel compositions of the present invention is achieved by presence in the pre-gel of one or more cross-linking agent comprising a multifunctional unsaturated fre-radically polymerisable compound. Conventional cross-linking agents are suitably used. The cross-linking provides the necessary mechanical stability and controls the adhesive properties of the hydrogel. The amount of cross-linking agent required will be readily apparent to those skilled in the art such as from about 0.01% to about 0.5%, particularly from about 0.05% to about 0.4%, most particularly from about 0.08% to about 0.3%, by weight of the total polymerisation reaction mixture. Typical cross-linkers include tripropylene glycol diacrylate, ethylene glycol dimethacrylate, triacrylate, polyethylene glycol diacrylate (polyethylene glycol (PEG) molecular weight between about 100 and about 4000, for example PEG400 or PEG600), and methylene bis acrylamide.

Organic Plasticiser

The one or more organic plasticiser, when present, may suitably comprise any of the following either alone or in combination: at least one polyhydric alcohol (such as glycerol, polyethylene glycol, or sorbitol), at least one ester derived therefrom, at least one polymeric alcohol (such as polyethylene oxide) and/or at least one mono- or poly-alkylated derivative of a polyhydric or polymeric alcohol (such as alkylated polyethylene glycol). Glycerol is the preferred plasticiser. An alternative preferred plasticiser is the ester derived from boric acid and glycerol. When present, the organic plasticiser may comprise up to about 45% by weight of the hydrogel composition.

Surfactant

Any compatible surfactant may optionally be used as an additional ingredient of the hydrogel composition. Surfactants can lower the surface tension of the mixture before polymerisation and thus aid processing. Non-ionic, anionic and cationic surfactants are preferred. The surfactant ideally comprises any of the surfactants listed below either alone or in combination with each other and/or with other surfactants. The total amount of surfactant, if present, is suitably up to about 10% by weight of the hydrogel composition, preferably from about 0.05% to about 2% by weight, more preferably from about 0.05% to about 1% by weight.

1. Non-ionic Surfactants

Suitable non-ionic surfactants include, but are not limited to, those selected from the group consisting of the condensation products of a higher aliphatic alcohol, such as a fatty alcohol, containing about 8 to about 20 carbon atoms, in a straight or branched chain configuration, condensed with about 3 to about 100 moles, preferably about 5 to about 40 moles and most preferably about 5 to about 20 moles of ethylene oxide. Examples of such non-ionic ethoxylated fatty alcohol surfactants are the Tergitol™ 15-S series from Union Carbide and Brij™ surfactants from ICI. Tergitol™ 15-S surfactants include C_{11}-C_{15} secondary alcohol polyethyleneglycol ethers. Brij™ 58 surfactant is polyoxyethylene(20) cetyl ether, and Brij™ 76 surfactant is polyoxyethylene(10) stearyl ether.

Other suitable non-ionic surfactants include, but are not limited to, those selected from the group consisting of the polyethylene oxide condensates of one mole of alkyl phenol containing from about 6 to 12 carbon atoms in a straight or branched chain configuration, with about 3 to about 100 moles of ethylene oxide. Examples of non- ionic surfactants are the Igepal™ CO and CA series from Rhone-Poulenc. Igepal™ CO surfactants include nonylphenoxy poly(ethyleneoxy) ethanols. Igepal™ CA surfactants include octylphenoxy poly(ethyloneoxy) ethanols.

Another group of usable non-ionic surfactants include, but are not limited to, those selected from the group consisting of block copolymers of ethylene oxide and propylene oxide or butylene oxide. Examples of such non-ionic block copolymer surfactants are the Pluronic™ and Tetronic™ series of surfactants from BASF. Pluronic™ surfactants include ethylene oxide-propylene oxide block copolymers. Tetronic™ surfactants include ethylene oxide-propylene oxide block copolymers. The balance of hydrophobic and hydrophilic components within the surfactant together with the molecular weight are found to be important. Suitable examples are Pluronic L68 and Tetronic 1907. Particularly suitable examples are Pluronic L64 and Tetronic 1107.

Still other satisfactory non-ionic surfactants include, but are not limited to, those selected from the group consisting of sorbitan fatty acid esters, polyoxyethylene sorbitan fatty acid esters and polyoxyethylene stearates. Examples of such fatty acid ester non- ionic surfactants are the Span™, Tween™, and Myrj™ surfactants from ICI. Span™ surfactants include C_{12}-C_{18} sorbitan monoesters. Tween™ surfactants include poly(ethylene oxide) C_{12}-C_{18} sorbitan monoesters. Myrj™ surfactants include poly(ethylene oxide) stearates.

2. Anionic Surfactants

Anionic surfactants normally include a hydrophobic moiety selected from the group consisting of (about C_6 to about C_{20}) alkyl, alkylaryl, and alkenyl groups and an anionic group selected from the group consisting of sulfate, sulfonate, phosphate, polyoxyethylene sulfate, polyoxyethylene sulfonate, polyoxyethylene phosphate and the alkali metal salts, ammonium salts, and tertiary amino salts of such anionic groups.

Anionic surfactants which can be used in the present invention include, but are not limited to. those selected from the group consisting of (about C_6 to about C_{20}) alkyl or alkylaryl sulfates or sulfonates such as sodium lauryl sulfate (commercially available as Polystep™ B-3 from Srepan Co.) and sodium dodecyl benzene sulfonate, (commercially available as Siponate™ DS-10 from Rhone-Poulenc);

polyoxyethylene (about C_6 to about C_{20}) alkyl or alkylphenol ether sulfates with the ethylene oxide repeating unit in the surfactant below about 30 units, preferably below about 20 units, most preferably below about 15 units, such as Polystep™ B-1 commercially available from Stepan Co. and Alipal™ EP110 and 115 from Rhone-Poulenc; (about C_6 to about C_{20}) alkyl or alkylphenoxy poly (ethyleneoxy)ethyl mono-esters and di-esters of phosphoric acid and its salts, with the ethylene oxide repeating unit in the surfactant below about 30 units, preferably below about 20 units, most preferably below about 15 units, such as Gafac™ RE-510 and Gafac™ RE-610 from GAF.

3. Cationic Surfactants

Cationic surfactants useful in the present invention include, but are not limited to, those selected from the group consisting of quaternary ammonium salts in which at least one higher molecular weight group and two or three lower molecular weight groups are linked to a common nitrogen atom to produce a cation, and wherein the electrically-balancing anion is selected from the group consisting of a halide (bromide, chloride, etc.), acetate, nitrite, and lower alkosulfate (methosulfate etc.). The higher molecular weight substituent(s) on the nitrogen is/are often (a) higher alkyl group(s), containing about 10 to about 20 carbon atoms, and the lower molecular weight substituents may be lower alkyl of about 1 to about 4 carbon atoms, such as methyl or ethyl, which may be substituted, as with hydroxy, in some instances. One or more of the substituents may include an aryl moiety or may be replaced by an aryl, such as benzyl or phenyl.

In a preferred embodiment of the invention the surfactant comprises at least one propylene oxide/ethylene oxide block copolymer, for example such as that supplied by BASF Plc under the trade name Pluronic P65 or L64.

Other additives

Additional polymer(s), typically rheology modifying polymer(s), may be incorporated into the polymerisation reaction mixture at levels typically up to

about 10% by weight of total polymerisation reaction mixture, e.g. from about 0.2% to about 10% by weight. Such polymer(s) may include polyacrylamide, poly-NaAMPS, polyethylene glycol (PEG), polyvinylpyrrolidone (PVP) or carboxymethyl cellulose.

A particularly preferred application is in the field of biomedical skin electrodes. When the hydrogels are intended for use in conjunction with Ag/AgCl medical electrodes, chloride ions are required to be present in order for the electrode to function. Potassium chloride and sodium chloride are commonly used. However any compound capable of donating chloride ions to the system may be used, for example, lithium chloride, calcium chloride, magnesium chloride or ammonium chloride. The amount that should be added is dependent on the electrical properties required and is typically about 0.5-8% by weight.

In general, an electrolyte (e.g. a salt such as a chloride as mentioned above or another salt such as a nitrate, for example calcium nitrate) will need to be included in the polymerisation reaction mixture in appropriate amounts, when the process is used to manufacture a hydrogel composition for use in an electrode.

The compositions prepared according to the present invention are used in biomedical electrodes in generally conventional manner, as will be readily understood by those skilled in this art.

Additional functional ingredients may also incorporated in the reaction mixture used in the invention, including bioactive compounds such as antimicrobial agents (e.g. citric acid, stannous chloride), enzymes, compounds providing a heating or cooling sensation to a patient's body, dermatologically active compounds and, for drug delivery applications, pharmaceutically active agents, the latter being designed to be delivered either passively (e.g. transdermally) or actively (e.g. iontophoretically) through the skin.

For use in pharmaceutical delivery devices for the delivery of pharmaceuticals or other active agents to or through mammalian skin, the compositions may

optionally contain topical, transdermal or iontophoretic agents and excipients. The compositions may contain penetration-enhancing agents to assist the delivery of water or active agents into the skin. Non-limiting examples of penetration-enhancing agents for use in such applications include methyl oleic acid, isopropyl myristate, Azone®, Transcutol® and N-methyl pyrrolidone.

Polymerisation Conditions

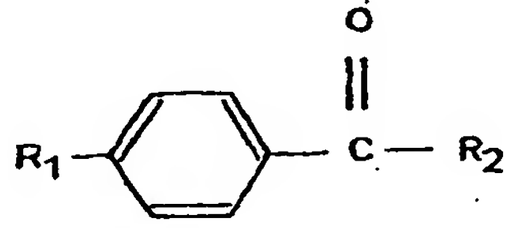
Any suitable free-radical polymerisation reaction may be used, according to the monomers present in the pre-gel. The range of reactions and their appropriate initiation and other conditions will be well known to those of ordinary skill in this art.

For example, the free-radical polymerisation may be initiated in generally known manner by light (photoinitiation), particularly ultraviolet light (UV photoinitiation); heat (thermal initiation); electron beam (e-beam initiation); ionising radiation, particularly gamma radiation (gamma initiation); non-ionising radiation, particularly microwave radiation (microwave initiation); or any combination thereof. The pre-gel mixture may include appropriate substances (initiators), at appropriate levels, e.g. up to about 5% by weight, more particularly between about 0.002% and about 2% by weight, for example between about 0.05% and about 2% by weight, which serve to assist the polymerisation and its initiation, in generally known manner.

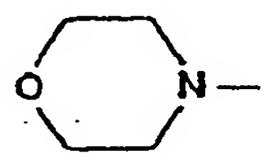
In one embodiment, the process of the invention involves free-radical polymerisation and the use of a photoinitiator or a combination of photo- and other initiation. Preferably the reaction mixture comprises an amount of photoinitiator of from about 0.003% to about 0.5%, and particularly from about 0.003% to about 0.4%, most particularly from about 0.009% to about 0.2%, by weight of the total polymerisation reaction mixture. If desired, the low levels of photoinitiator described in PCT Patent Application No. WO-01/96422 may be used. Preferred photoinitiators include any of the following either alone or in combination:

Type I-α-hydroxy-ketones and benzilidimethyl-ketals e.g. Irgacure 651. These are believed on irradiation to form benzoyl radicals that initiate polymerisation. Photoinitiators of this type that are preferred are those that do not carry substituents in the *para* position of the aromatic ring. Examples include Irgacure184 and Daracur 1173 as marketed by Ciba Chemicals, as well as combinations thereof.

Photoinitiators of the following general formula are preferred:



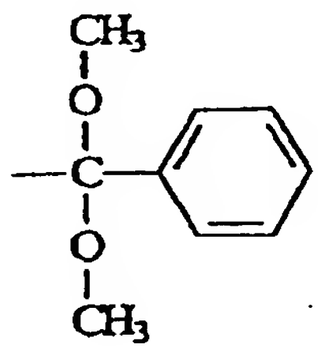
where R_1 can be any of the following:- hydrogen, H_3C-S- ,

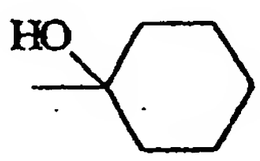


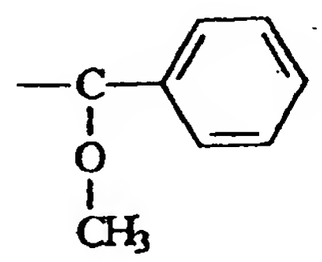
or

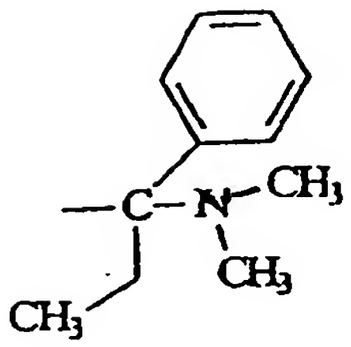
R_1 is most preferably hydrogen.

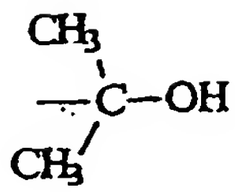
R_2 can suitably be any of the following:-

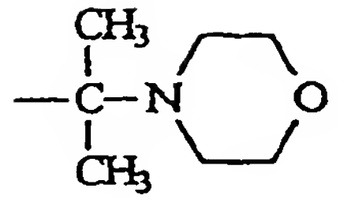




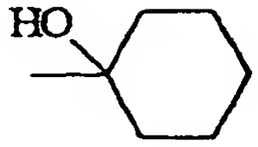








R_2 is most preferably as follows:-



A particularly preferred photoinitiator is 1-hydroxycyclohexyl phenyl ketone; for example, as marketed under the trade name Irgacure 184 by Ciba Speciality Chemicals. Also preferred are Daracur 1173 (2-hydroxy-2-propyl phenyl ketone) and mixtures of Irgacure 184 and Daracur 1173.

In preparing hydrogel compositions in accordance with the invention, the ingredients will be mixed to provide a reaction mixture in the form of an initial pre-gel formulation, which is most preferably a liquid, and this is then converted into a hydrogel by a free-radical polymerisation reaction. As mentioned above, air bubbles may be introduced into the pre-gel prior to the polymerisation reaction, for example by mechanical agitation of the pre-gel, where it is desired to produce a hydrogel mass having an internal cellular structure.

Photo-polymerisation is particularly suitable, and may be achieved using photoinitiators, optionally together with other initiators, such as heat and/or ionizing radiation. Photoinitiation will usually be applied by subjecting the pre-gel reaction mixture containing an appropriate photoinitiation agent to ultraviolet (UV) light after it has been spread or coated as a layer on siliconised release paper or other solid substrate. The incident UV intensity, at a wavelength in the range

from 240 to 420nm, is typically greater than about 10mW/cm^2. The processing will generally be carried out in a controlled manner involving a precise predetermined sequence of mixing and thermal treatment or history.

The UV irradiation time scale should ideally be less than 60 seconds, and preferably less than 10 seconds to form a gel with better than 95% conversion of the monomers. Those skilled in the art will appreciate that the extent of irradiation will be dependent on a number of factors, including the UV intensity, the type of UV source used, the photoinitiator quantum yield, the amount of monomer present, the nature of the monomer(s) present, the presence of dissolved oxygen, the presence of polymerisation inhibitor, the thickness of the reaction mixture when coated onto the substrate and the nature of substrate onto which the reaction mixture is coated.

Applications

The hydrogel compositions described herein may suitably be used in a range of skin contact or covering applications where the composition is brought into contact either with skin or with an intermediary article which interfaces between the composition and the skin. The composition may be unsupported or may be supported on a backing structure. The compositions may suitably be in the form of sheets, coatings, membranes, composites or laminates. Such applications include patches, tapes, bandages, devices and dressings of general utility or for specific uses, including without limitation biomedical, skin care, personal and body care, palliative and veterinary uses such as, for example, skin electrodes; wound and burn healing; wound and burn management; skin cooling; skin moisturising; skin warming; aroma release or delivery; decongestant release or delivery; pharmaceutical and drug release or delivery; perfume release or delivery; fragrance release or delivery; scent release or delivery; adhesive use, e.g. in skin contacting devices, ostomy and related incontinence devices, and the like.

The hydrogel compositions prepared according to the present invention are used in these applications in generally conventional manner, as will be readily understood by those skilled in this art.

Examples of the Invention

The invention will be further described with reference to the following Examples, which all relate to the preparation of hydrogels having an internal cellular structure and should not be understood to limit the scope of the invention.

General Preparative Method

The appropriate weight of acryloyl morpholine ("ACMO") was added to the appropriate weight of water (Examples 1 to 22, 24, 25, 30, 31 to 34) or to the aqueous saturated or supersaturated liquid formed by gentle warming of a hydrated salt (see further details below) to about 60°C (Examples 23, 26 to 29, 32 and 33). The surfactant Pluronic 65 ("P65") was added to each aqueous composition thereby obtained.

For Examples 18, 19, 26 and 28, acrylic acid ("AA") comonomer was also added with the ACMO. For Example 9, 2-acrylamido-2-methylpropane sulphonic acid sodium salt (NaAMPS) was also added with the ACMO (see discussion below). For Examples 24, 25, 30 and 32 to 34, a salt (see further details below) was also added, if necessary with gentle warming. For Examples 23 to 34, the salt was selected from calcium chloride hexahydrate Examples 23 to 28), calcium nitrate tetrahydrate (Examples 29 and 30), a 50:50 weight mixture of calcium chloride hexahydrate and calcium nitrate tetrahydrate (Example 31), sodium chloride (Example 32) and magnesium chloride hexahydrate (Examples 33 and 34). The amounts of the AA and the salt are indicated in the table below. The appropriate weight of glycerol was added (Examples 5 to 15, 18 to 22, 27 and 28 only) and the mixture stirred for about 30 minutes. Amounts of these initial ingredients for Examples 1 to 22 are shown in parts by weight (normally out of 100, but out of 104 in the case of Example 9); amounts for Examples 23 to 34 are shown in grams.

A mixture of crosslinker ("XL") and photoinitiator ("PI") was made by adding the appropriate weight of IRR280 (PEG400 diacrylate, UCB Chemicals) ("280") to the appropriate weight of photoinitiator, Daracur 1173 (Ciba Specialty Chemicals) ("1173"). The appropriate amount of this liquid mixture was added to the mixture, which was stirred for 1 hour, covered to exclude light. The figures for Examples 1 to 9, 12 and 16 to 20 in the table below show the percentage by weight of the initial mixture, at which the PI/XL mixture (6 parts by weight PI: 20 parts by weight XL) is added. The figures for Examples 10, 21 and 22 in the table below show the percentage by weight of the initial mixture, at which the PI/XL mixture (10 parts by weight PI: 20 parts by weight XL) is added. The figure for Example 11 in the table below shows the percentage by weight of the initial mixture, at which the PI/XL mixture (100.7 parts by weight PI: 108 parts by weight XL) is added. The figure for Example 13 in the table below shows the percentage by weight of the initial mixture, at which the PI/XL mixture (1 parts by weight PI: 3 parts by weight XL) is added. The figure for Example 14 in the table below shows the percentage by weight of the initial mixture, at which the PI/XL mixture (9 parts by weight PI: 10 parts by weight XL) is added. The figure for Example 15 in the table below shows the percentage by weight of the initial mixture, at which the PI/XL mixture (35 parts by weight PI: 54 parts by weight XL) is added. The figures for Examples 23 to 34 in the table below show the weight of the PI/XL mixture (1 parts by weight PI: 10 parts by weight XL) added.

In each case the mixture was mechanically agitated with a high speed stirrer, to entrain air bubbles in the pre-gel. 50g of the mixture at a coat weight of 1.5kg/sq.m was cured in the laboratory on a tray lined with siliconised paper by passing at a speed of 7m/minute three times under ultra-violet (UV) radiation of 80W/cm from a medium pressure mercury vapour lamp.

Compositions

The ingredients of the compositions of Examples 1 to 34 are shown in the following table:

	Ex. 1	Ex. 2	Ex. 3	Ex. 4	Ex. 5	Ex. 6	Ex. 7	Ex. 8	Ex. 9
ACMO	35	35	35	35	35	35	35	35	35
Water	65	65	65	65	50	30	20	10	10
Glycerol	0	0	0	0	15	35	45	55	55
PI/XL	0.1	0.2	0.3	0.4	0.4	0.4	0.4	0.4	0.4
Na/AMPS	0	0	0	0	0	0	0	0	4
P65	2	2	2	2	2	2	2	2	2

	Ex. 10	Ex. 11	Ex. 12	Ex. 13	Ex. 14	Ex. 15	Ex. 16	Ex. 17
ACMO	35	35	35	35	35	35	20	20
Water	20	20	20	20	20	20	80	80
Glycerol	45	45	45	45	45	45	0	0
PI/XL	0.3	0.21	0.147	0.41	0.18	0.16	0.30	0.40
P65	2	2	2	2	2	2	2	2

	Ex. 18	Ex. 19	Ex. 20	Ex. 21	Ex. 22	Ex. 23	Ex. 24	Ex. 25
ACMO	30	30	35	35	35	1.5g	1.5g	2g
Water	28	28	20	20	20	0g	2g	8g
Glycerol	40	40	45	45	45	0g	0g	0g
PI/XL	0.35	0.25	0.40	0.30	0.15	0.03g	0.03g	0.03g
AA	2	2	0	0	0	0g	0g	0g
Salt	0	0	0	0	0	10g	8g	2g
P65	2	2	2	2	2	0.2g	0.2g	0.2g

	Ex. 26	Ex. 27	Ex. 28	Ex. 29	Ex. 30	Ex. 31	Ex. 32	Ex. 33	Ex. 34
ACMO	1g	1.5g	2.5g	1.5g	1.5g	1.5g	2g	1.5g	1.5g
Water	0g	0g	0g	0g	2g	0g	8g	3g	2.3g
Glycerol	0g	0.75g	1.5g	0g	0g	0g	0g	0g	0g
PI/XL	0.03g	0.03g	0.03g	0.03g	0.03g	0.03g	0.03g	0.03g	0.03g
AA	0.5g	0g	0.5g	0g	0g	0g	0g	0g	0g
Salt	10g	10g	20g	10g	8g	10g	2g	7g	7.7g
P65	0.2g	0.2g	0.1g	0.2g	0.2g	0.2g	0.2g	0.2g	0.2g

Results and Discussion

Example 1 gave a gel which was clear and colourless, soft and leggy. Example 2 gave a gel which was clear and colourless, a nice soft gel. Example 3 gave a gel which was clear, colourless and tough. Example 4 gave a gel which was clear and colourless, a tough and brittle gel. Example 5 gave a gel which was clear and colourless, tough and slightly tacky. Examples 6 and 7 gave gels which were clear and colourless, tough and tacky. All the above gels were acceptable.

Example 8 gave a gel which was white, hard and brittle and showed syneresis of the glycerol. This gel was unacceptable for use as a bioadhesive. It is believed that this unacceptability may be more generally observed at very high levels of organic plasticiser. However, as shown by Example 9, the problem is surprisingly and effectively overcome by the presence of a small amount of the ionic comonomer (NaAMPS) in the pre-gel. Example 9 gave an acceptable clear, colourless, tough gel.

Example 10 gave a gel which was clear and colourless, soft and tacky. Examples 11 and 12 gave gels which were leggy. Example 13 gave a gel which was clear and colourless, tough, tacky and brittle. Examples 14 and 15 gave clear leggy gels. Example 15 gave a gel which was soft, clear and leggy. Example 17 gave a gel which was clear but brittle. Example 18 gave a gel which was clear and strong. Example 19 gave a gel which was clear but soft. Examples 20 to 22 gave gels which were clear and slightly tacky. Examples 23 to 34 gave acceptable gels, many of which displayed substantial robustness under extremes of temperature and atmospheric dryness. In summary, all of Examples 10 to 34 produced acceptable gels.

The above broadly describes the present invention without limitation. Variations and modifications as will be readily apparent to those of ordinary skill in this art are intended to be included in the scope of this application and subsequent patents.

CLAIMS

1. A hydrogel composition comprising a plasticised cross-linked hydrophilic polymer of acryloyl morpholine and optionally one or more comonomers.

2. A hydrogel composition according to claim 1, wherein the acryloyl morpholine is N-acryloyl morpholine.

3. A hydrogel composition according to claim 1 or claim 2, wherein the composition is plasticised by water, a mixture of water and a water-miscible organic plasticiser, or an organic plasticiser.

4. A hydrogel composition according to claim 3, wherein the organic plasticiser is selected from: at least one polyhydric alcohol; at least one ester derived therefrom; at least one polymeric alcohol; at least one mono- or poly-alkylated derivative of a polyhydric or polymeric alcohol; and mixtures thereof.

5. A hydrogel composition according to any one of the preceding claims, wherein the organic plasticiser is glycerol or a mixture of water and glycerol.

6. A hydrogel composition according to any one of the preceding claims, wherein the one or more comonomers, when present, are selected from: 2-acrylamido-2-methylpropane sulphonic acid or an analogue thereof or a salt thereof; acrylic acid or an analogue thereof or a salt thereof; a polymerisable sulphonate or a salt thereof; acrylamide or a mono- or di-N-alkylacrylamide or an analogue thereof; and mixtures thereof.

7. A hydrogel composition according to any one of the preceding claims, wherein the one or more comonomers, when present, are selected from: 2-acrylamido-2-methylpropane sulphonic acid; an ammonium or alkali metal salt of 2-acrylamido-2-methylpropane sulphonic acid; acrylic acid (3-sulphopropyl) ester; a salt of acrylic acid (3-sulphopropyl) ester; diacetone acrylamide; a vinyl lactam; an N-alkylated acrylamide; an N,N-dialkylated acrylamide; N-vinyl pyrrolidone; and mixtures thereof.

8. A hydrogel composition according to any one of the preceding claims, further including one or more additives selected from surfactants, polymers, electrolytes, chloride sources, bioactive compounds, personal and body care agents, and mixtures thereof.

9. A hydrogel composition according to any one of the preceding claims, wherein the hydrogel contains more than about 40% by weight of water.

10. A hydrogel composition according to claim 9, wherein the hydrogel contains between about 60% and about 95% by weight of water.

11. A hydrogel composition according to claim 9, wherein the hydrophilic polymer is cross-linked by the presence of the photopolymerisation product of a multifunctional free-radically photopolymerisable compound and the hydrogel contains at least about 0.05 by weight of a photoinitiator.

12. A hydrogel composition according to any one of the preceding claims, which has sufficient human skin adhesion and flexibility to conform and adhere to human skin contours and/or the contours of an article to which the hydrogel composition is attached after storage in a surrounding atmosphere at substantially any temperature within the temperature range of substantially -10°C to +30°C and/or at substantially any atmospheric humidity within the range from substantially bone dry to 100% relative humidity.

13. A hydrogel composition according to claim 12, wherein the said skin adhesion and flexibility is maintained in storage for a period of at least about two weeks under the said temperature and dryness conditions.

14. A hydrogel composition according to any one of the preceding claims, comprising an internal cellular structure which is closed cell, open cell or any combination thereof.

15. A hydrogel composition according to any one of the preceding claims, in the form of a sheet having first and second major faces.

16. A hydrogel composition according to claim 15, wherein each of the first and second major faces is in contact with a protective release layer.

17. A hydrogel composition according to claim 15, wherein one of the first and second major faces is in contact with a protective release layer and the other of the first and second major faces is in contact with a backing member.

18. A hydrogel composition according to claim 17, wherein the backing member is a member forming part of a wound or burn dressing, a biomedical electrode or another article where a bioadhesive hydrogel layer is to be provided in use between the article and the skin of a wearer.

19. A hydrogel composition according to any one of the preceding claims, consisting essentially of a cross-linked hydrophilic polymer of N-acryloyl morpholine and optionally one or more comonomers, together with water and/or one or more organic plasticiser, and optionally together with one or more additives selected from surfactants, polymers, electrolytes, chloride sources, bioactive agents, personal and body care agents, and mixtures thereof, with less than about 10% by weight of other additives.

20. A process for the preparation of a hydrogel composition according to any one of the preceding claims, which comprises free-radically polymerising a mixture comprising: (1) acryloyl morpholine and optionally one or more comonomer; and (2) one or more cross-linking agent comprising a multifunctional unsaturated free-radically polymerisable compound; the polymerisation being conducted in the presence or absence of a plasticiser, with the proviso that when the polymerisation is conducted in the absence of a plasticiser, a plasticiser is added to the polymer product of the polymerisation.

21. A process according to claim 20, wherein the acryloyl morpholine is N-acryloyl morpholine.

22. A process according to claim 20 or claim 21, wherein the polymerisation is a photopolymersiation carried out in the presence of a photoinitiator.

23. A process according to any one of claims 20 to 22, wherein the mixture on which the polymerisation is carried out consists of an aqueous composition of the components in which a salt is present in a condition of substantial saturation or supersaturation.

24. A process according to claim 23, wherein the mixture on which the polymerisation is carried out is obtained by initially warming a hydrated form of the salt to a temperature at which the salt dissolves in its water of crystallisation, and subsequently adding non-aqueous components of the mixture to the substantially saturated or supersaturated salt solution thereby obtained.

25. A process according to any one of claims 20 to 24, wherein substantially all of the components of the hydrogel present in the mixture immediately before the polymerisation are also present, whether in original or polymerised or otherwise chemically modified form, in the composition resulting from the polymerisation.

26. A process according to any one of claims 20 to 25, which includes the step of introducing air bubbles into the pre-polymerisation mixture.

27. A process according to claim 26, wherein the air bubbles are introduced by mechanical agitation of the pre-polymerisation mixture under an air atmosphere.

28. Use of a bioadhesive hydrogel composition, comprising a plasticised cross-linked hydrophilic polymer of N-acryloyl morpholine and optionally one or more comonomers, in the bioadhesive portion of a bioadhesive article to be adhered in use to human skin, for the technical purpose of enabling said bioadhesive article to be stored and transported for time periods of at least about two weeks under any temperature within the temperature range of substantially -10°C to +30°C and/or any surrounding atmospheric humidity within the humidity range of substantially bone dry to 100% relative

humidity and thereafter providing in use sufficient human skin adhesion for the intended use and sufficient flexibility to conform to human skin contours and/or to contours of the articles for the intended use.

INTERNATIONAL SEARCH REPORT

Interr ıl Application No
PCT/GB 02/05681

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61L15/24 C08F20/58

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C08F A61L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, MEDLINE, PAJ, WPI Data, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 01 96422 A (DONNELLY MICHAEL JOSEPH ;MUNRO HUGH SEMPLE (GB); PAGE ALISON (GB);) 20 December 2001 (2001-12-20) cited in the application page 6, line 5; claims	1-28
X	WO 00 45864 A (MUNRO HUGH SEMPLE ;FIRST WATER LTD (GB)) 10 August 2000 (2000-08-10) page 29, line 10 -page 33, line 7; claims 1-49	1-28
X	GB 1 323 809 A (CESKOSLOVENSKA AKADEMIE VED) 18 July 1973 (1973-07-18) column 3, line 1; claim 1; examples 1,2,5	1-3, 9-11, 20-22

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
9 April 2003	16/04/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Winger, R

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inter al Application No
PCT/GB 02/05681

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 717 049 A (LIAO XIUGAO ET AL) 10 February 1998 (1998-02-10) claims 1,3,18 ----	1-3, 9-11,15, 20-22

INTERNATIONAL SEARCH REPORT

Inte al Application No
PCT/GB 02/05681

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 0196422 A	20-12-2001	AU	6413101 A	24-12-2001
		EP	1292628 A1	19-03-2003
		WO	0196422 A1	20-12-2001
WO 0045864 A	10-08-2000	AU	2306100 A	25-08-2000
		CA	2361871 A1	10-08-2000
		EP	1150721 A1	07-11-2001
		WO	0045864 A1	10-08-2000
		JP	2002536073 T	29-10-2002
		US	2002026005 A1	28-02-2002
GB 1323809 A	18-07-1973	CS	149376 B1	05-07-1973
		AU	3475171 A	03-05-1973
		CA	936998 A1	13-11-1973
		DE	2151909 A1	27-04-1972
		FR	2111524 A5	02-06-1972
		IT	946004 B	21-05-1973
		JP	50007112 B	20-03-1975
		US	3876594 A	08-04-1975
US 5717049 A	10-02-1998	AU	712171 B2	28-10-1999
		AU	2040497 A	17-10-1997
		BR	9708263 A	04-01-2000
		CA	2249991 A1	02-10-1997
		CN	1219179 A ,B	09-06-1999
		EP	0889916 A1	13-01-1999
		WO	9735896 A1	02-10-1997
		JP	2000507298 T	13-06-2000
		KR	2000004956 A	25-01-2000
		NZ	331946 A	27-03-2000